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RESEARCH ARTICLE

Parathyroid Hormone as a Predictor of Post Total Thyroidectomy Parathyroid Gland Injury

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ABSTRACT

Background: Post-thyroidectomy hypocalcaemia is one of the most prevalent morbidities. Serum parathormone hormone (PTH) levels before and after the operation have been an area of high interest for detecting the risk of postoperative hypocalcaemia. **Aim:** This study was conducted to determine the accuracy of perioperative parathormone hormone assessment as a predictor of parathyroid gland injury in total thyroidectomy operations. **Methods:** Fifty patients presented with goiter indicated for total thyroidectomy operation were evaluated and operated. Routine preoperative labs with measurement of the parathormone hormonal level, thyroid profile, and serum calcium (Ca) were done. **Results:** The level of postoperative PTH was lower in patients with post-operative manifestations of hypocalcaemia than those without (6.3 ± 5.1 vs. 24.8 ± 6.7), with a 78.9% drop in PTH from the preoperative level in the hypocalcaemia group versus 56.1% drop in the normocalcemia group ($P < 0.0001$). Percentage changes in PTH had good discriminative power, AUC=0.840 (95% CI: 0.648-1.000), $p=0.002$. **Conclusion:** postoperative PTH levels can be a good predictor of hypocalcemia in total thyroidectomies. Patients with a greater than 64.8% decrease in PTH levels were significantly more likely to develop hypocalcemia.

Keywords: hypocalcemia; predictor; PTH; thyroidectomy

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INTRODUCTION

Post-thyroidectomy hypocalcemia is one of the most prevalent morbidities; the incidences of transient and permanent hypocalcaemia range from 2 to 32% (Grodski et al., 2008; Lee et al., 2015; Seo et al., 2015) and 0.2 to 13% (Seo et al., 2015; Testini et al., 2017), respectively, in patients that have undergone total thyroidectomy.

Hypocalcaemia after thyroidectomy is caused by direct injury to the parathyroid gland or injury to its blood supplies. Post-operative hypocalcaemia affects the physical and psychological health of the patient and lengthens the hospital stay (Reeve and Thompson, 2000). Hypocalcaemia can be present with perioral numbness, numbness of the fingertips, and a positive of Chovestek's sign. There may be muscle spasms, cramping, seizures, or cardiac arrhythmia in severe cases. Treatment of hypocalcaemia consists of giving patients calcium supplements and vitamin D (Falk et al., 2013).

Accurate prediction of risk has the potential to influence management strategies and could reduce the risk of this complication. Edafe et al. 2016 has demonstrated that perioperative parathormone hormone (PTH) concentration, preoperative vitamin D level, and early postoperative changes in calcium levels are useful biochemical predictors of post-thyroidectomy hypocalcaemia. Clinical predictors of transient hypocalcaemia include female sex, Graves' disease, PTG auto-transplantation, and inadvertent parathyroid gland (PTG) excision. Post-operative PTH level can be used to stratify the risk of patients developing hypocalcaemia after thyroidectomy (Wiseman et al., 2010). Comparison of serum PTH levels before and after the operation with different techniques has been an area of high interest for researchers to yield promising results for detecting the risk of postoperative hypocalcaemia (Lombardi et al., 2016).

The current study aims to determine the accuracy of perioperative (pre and post-operative) parathormone hormone assessment as a single predictor of parathyroid gland injury in total thyroidectomy operations.

PATIENTS AND METHODS

This cross-sectional study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and after the approval of the local ethics committee (M408/95 on 14/4/2019). Informed consent was obtained from all study subjects after the nature of the study was explained. The study was conducted as a prospective on 50 cases presented with goiter with formal surgical indication for total thyroidectomy operation. They were evaluated, operated and included in this study in the period from May 2019 to November 2019.

Patients were examined at our outpatient general surgery clinic in Fayoum University Hospitals and further medical evaluations were completed in our inpatient ward. The sample size was computed using G-Power© software version 3.1.9; assuming a moderate effect size (0.50) for the difference between pre and postoperative PTH, two-sided (two tails) type I error 0.05 and power of 90%, 47 Subjects were calculated. To overcome the problem of loss of follow-up cases were increased by 10% to reach 50 cases.

Inclusion Criteria

- Patients aged 18 years or older.
- Patients planned for total thyroidectomy.
- Patients fit for general anesthesia.

Exclusion criteria

- Patients unfit for general anesthesia.
- Patients with uncontrolled comorbidities as diabetes, nutritional deficiencies, malabsorption, and renal disease.
- Pregnant and lactating females.
- Patients receiving medications that affect blood calcium and hormone levels.

Perioperative evaluation included

- **History:** Besides the routine history that was taken from all the patients, special attention was given to take accurate history regarding drug intake, previous surgeries, and manifestations suggestive of hypoparathyroidism, hyperparathyroidism, and malignancy.
- **General examination:** Routine general examination with careful examination of signs suggestive of hypoparathyroidism, hyperparathyroidism, and malignancy.
- **Neck examination:** Classic clinical neck examination with careful examination of the draining lymph nodes and retrosternal extension.
- **Laboratory investigations:** Routine preoperative labs with measurement of the parathormone hormonal levels (within 24 hours before and after surgery/Reference range 10-65 pg/ml), thyroid profile, and serum calcium (Ca) (within 24 hours before and after surgery/ Reference range 8.8-10.6 mg/dl)
- **Imaging:** Neck ultrasound as routine preoperative imaging for all cases. Thyroid scan for all thyrotoxic patients presented with a solitary or dominant thyroid nodule.
- **Pathological:** Fine needle aspiration cytology (FNAC) was done for the cases presented with positive cervical LNs either clinically or by Ultrasound or with a history suggestive of malignancy.

Post-operative care

Postoperative care was made of clinical and laboratory components, clinical follow-up was directed within the first 24 h mainly towards the observation of the postoperative bleeding and voice changes and manifestations of hypoparathyroidism and hypocalcaemia. These manifestations that were collected for all the patients via the researcher included the following:

Symptoms

- Perioral paraesthesia.
- Digital numbness.
- Muscles cramps.

Signs

- Confusion, disorientation, delirium, and seizure.
- Chovstek sign (contraction of facial muscles provoked by lightly tapping over the facial nerve anterior to the ear as it crosses the zygomatic arch, this induces twitching of the homolateral facial muscles due to hyperexcitability of the nerve) (Young et al., 2014)
- Trousseau sign (is observable as a carpopedal spasm induced by ischemia secondary to the inflation of a sphygmomanometer cuff, commonly on an individual's arm, to 20 mmHg over their systolic blood pressure for 3 minutes, the carpopedal spasm, is visualized as flexion of the wrist, thumb, and metacarpophalangeal joints with hyperextension of the fingers) (Young et al., 2014)
- electrocardiography (ECG) (prolonged QT interval or arrhythmias) Auto transplant was done in two cases who had removal of parathyroid gland and no parathyroid glands found in all examined specimens by histopathology. Moreover, one of those two cases presented with manifestations of postoperative hypocalcemia which was managed with oral Ca and Vitamin D and improved.

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 22 (SPSS Inc, USA). For quantitative data, the mean and standard deviation (SD) were calculated. Paired t-test was performed to compare between values of PTH before and after the operation. An independent t-test was used in comparing between the two groups of calcium status as regards PTH. Qualitative data were presented as numbers and percentages and the Chi-square test was used as a test of significance. For interpretation of results of tests of significance, significance was adopted at P<0.05. The Receive Operating Characteristic (ROC) curve was used to determine the discrimination value of the absolute difference in PTH and percentage changes in PTH for predicting hypocalcaemia and to define the optimal cut-points for sensitivity and specificity.

RESULTS

Fifty total thyroidectomy cases were included in this study according to selection criteria with ages ranged from 28 to 63 years old (Mean 42.9 ± 7.7 years). Patient age ranged from 28 – 63 years old with a mean ± SD of 42.9 ± 7.7. As regards sex, most of the studied patients 34/50 (68.0%) were females and 16/50 (32.0%) were males. About one-fifth of studied patients, 9 (18.0%) developed manifestations of hypocalcaemia within the first 24 hours post-operative after thyroidectomy.

Table 2 demonstrated that PTH (post) was lower in patients with post-operative manifestations of hypocalcaemia than those without (6.3 ± 5.1 vs. 24.8 ± 6.7) This denoted a percent decline in PTH from the preoperative level by 78.9% in the hypocalcaemia group versus 56.1% in the group with normal calcium (P < 0.0001). The absolute difference in PTH had a poor discriminative power in predicting hypocalcaemia, AUC=0.569 (95% CI: 0.339-0.799), p=0.520. On the other hand, percentage changes in PTH had good discriminative power, AUC=0.840 (95% CI: 0.648-1.000), p=0.002. If sensitivity is preferred, the cut-off point of (-60.6) can be selected while if specificity is preferred, (-77.9) is more suitable as a cut-off point. The cut-off point of (-64.8) represents the most balanced point.

Table 1. Incidence of occurrence of manifestations of hypocalcaemia within the first 24 hours postoperative:

	N	%
Yes	9	18.0%
No	41	82.0%

Table 2. The difference in PTH according to hypocalcaemia

	Hypocalcaemia				P-value#
	Yes (N=9)		No (N=41)		
	Mean	SD	Mean	SD	
PTH (pre)	35.6	15.6	60.5	14.1	
PTH (post)	6.3	5.1	24.8	6.7	
% change	-78.9	16.8	-56.1	12.5	<0.0001*

Independent-t-test, *Significant

Table 3. PTH discriminative power in predicting hypocalcaemia

	AUC (95% CI)	P-value	Cut-off point	Sensitivity	Specificity
PTH Absolute	0.569 (0.339-0.799)	0.520	-35.7	67%	46.3%
PTH % change	0.840 (0.648-1.000)	0.002*	-77.9	66.7%	100%
			-64.8	77.8%	82.9%
			-60.6	88.9%	63.4%

*Significant

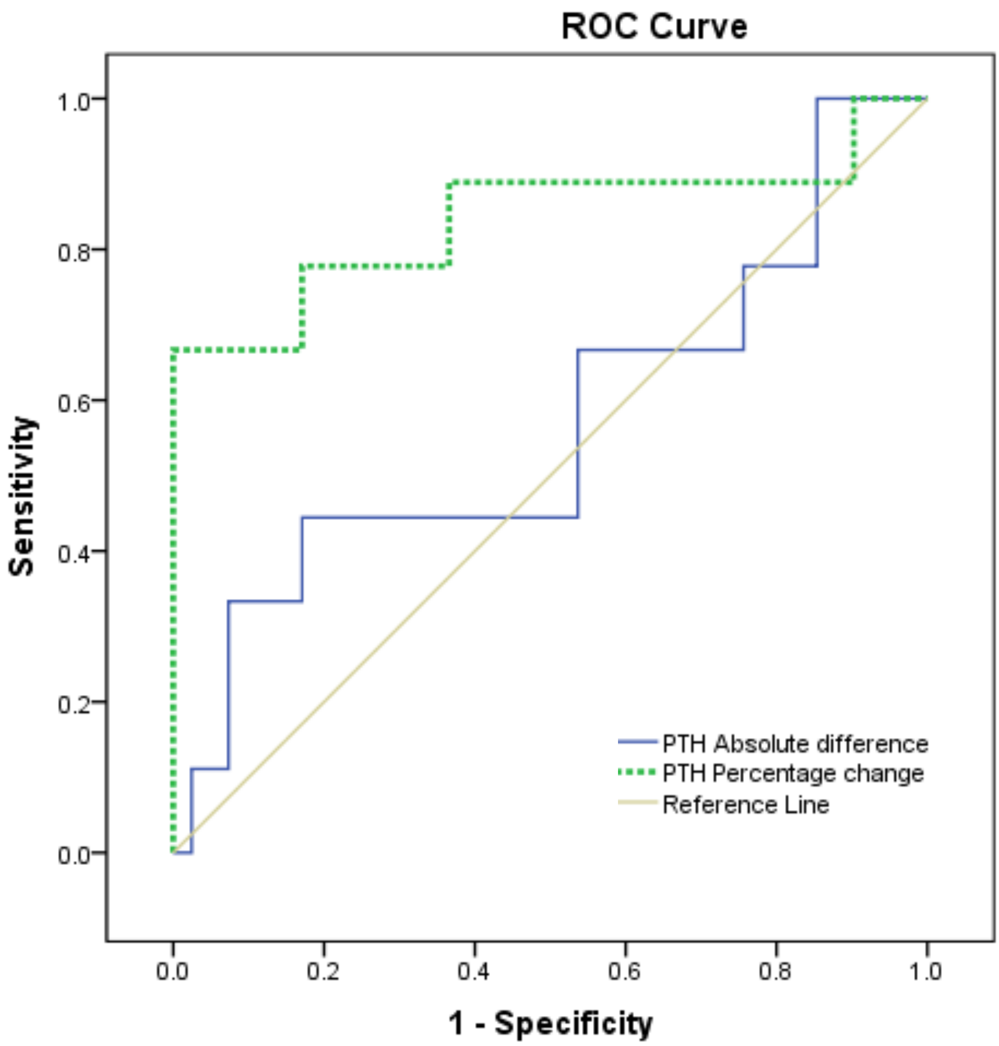

Figure 1. Receive operating characteristic (ROC) curve to determine the discrimination value of the absolute difference in PTH and percentage changes in PTH for predicting hypocalcaemia.

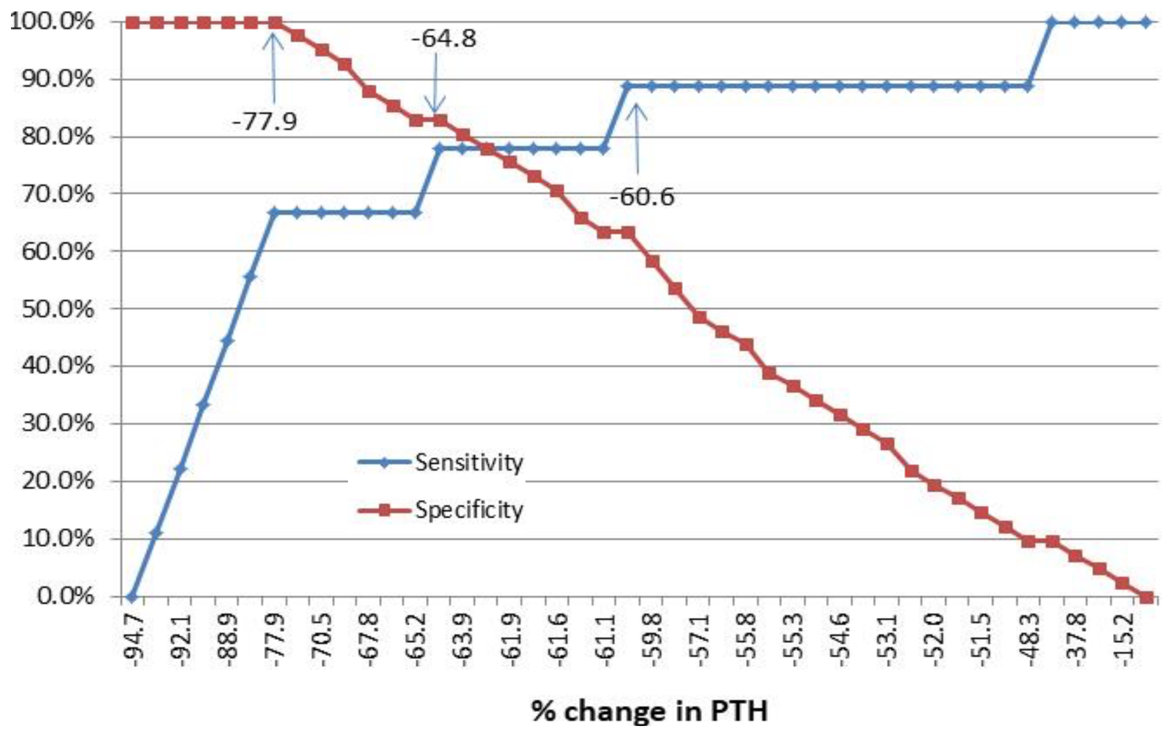

Figure 2. Plotting of sensitivity against specificity according to different cut-off points of % change in PTH to predict hypocalcaemia.

DISCUSSION

Hypoparathyroidism is seen as a common iatrogenic complication following surgical procedures to the neck, and commonly, to the thyroid gland. Despite many improvements in the surgical techniques to avoid hitting and damaging the parathyroid glands, hypoparathyroidism remains a very significant postoperative morbidity after total thyroidectomy. This specific complication, as well as recurrent laryngeal nerve injury, is feared, as it may give rise to significant and sometimes permanent, disability for the patient (Wang et al., 2016).

Several studies on post-surgical hypoparathyroidism suggest that this problem has a high impact on health and social life either for surgeons and patients. Costs to society in terms of medical treatment, follow-up, including frequent and repeated laboratory testing, treatment and sick leave, are considerable (Bilezikian et al., 2011). The success of rapid PTH determinations in parathyroid surgery led some of the investigators to evaluate its usefulness to predict the incidence of hypoparathyroidism following thyroid surgery (Sitges-Serra, 2010).

Post-thyroidectomy PTH levels within the first 24 hours postoperative accurately predict hypocalcaemia but lack 100% accuracy. Progressive and severe hypocalcaemia is unlikely in the setting of a normal PTH level and hence PTH can be used cautiously to facilitate discharge within 24 h for many patients (Grodski et al. 2008). Concerning the studies which investigated the optimal timing of the measurement, they did not show any difference between measurements taken at 10 minutes, 1, 4, 6, or 24 h. (Grodski et al., 2008).

In the current study, the postoperative PTH level was lower in patients with post-operative manifestations of hypocalcaemia than those without manifestations (6.3 ± 5.1 vs. 24.8 ± 6.7). This denoted a percent decline in PTH from the preoperative level by 78.9% in the hypocalcaemia group versus 56.1% in the group with normal calcium ($P < 0.0001$).

Higgins et al. 2014, demonstrated that 64% of those patients who subsequently required calcium supplementation had a decrease in PTH levels 20 minutes after surgery greater than 75% from preoperative, and 74% of those who did not need calcium supplementation demonstrated a decrease of less than 75% from preoperative. For Lombardi et al. 2004, PTH less than 10 pg/ml measured four to six hours after surgery predicted hypocalcaemia with an overall accuracy of 98%.

Depending on the threshold maintained, the single measurement of iPTH (intact PTH is the biologically active form) conflicts with a lack of sensitivity or specificity. In our study, the iPTHH4 (iPTH measured within 4 hours after surgery) level with the threshold of 19.4 ng/L was obtained with the ROC curve had a sensitivity of 84.6% and a specificity of 92.9% for predicting hypocalcemia.

Some authors proposed taking an iPTHH6 (iPTH measured within 6 hours after surgery) threshold of 28 ng/L, coupled with a corrected calcium level greater than 2.14 mmol/L at the same time, to obtain specificity and a positive predictive value of 100%. Nevertheless, their sensitivity and negative predictive values were 38.1% and 13.3%. To resolve this threshold problem, some authors studied the iPTH decline between its preoperatory value and postoperative value (Grodski et al., 2008; Lam and Kerr, 2013, Lombardi et al., 2004, Roh and Park, 2006; Toniato et al., 2008). In an analysis of 9 observational studies10 relevant to iPTH decline, investigators found that with a threshold of iPTHH6 decline of 65% sensitivity and specificity values were respectively 96.4% and 91.4%. With a threshold of iPTHH1-2 decline of 70%, sensitivity and specificity values were 93.3% and 88%, respectively. The thresholds of iPTH decline found in the different publications vary from 62.5–75.7% (Grodski et al., 2008; Lam and Kerr, 2013; Lombardi et al., 2004; Roh and Park, 2006; Toniato et al., 2008). Thus, calculation of the relative iPTH decline is reliable for allowing patients to be discharged at D1 without risk of hypocalcemia. It also allows one to distinguish between patients who will develop symptomatic hypocalcemia with good sensitivity and good specificity. We also found that absolute difference in PTH had a poor discriminative power in predicting hypocalcaemia, AUC=0.569 (95% CI: 0.339-0.799), p=0.520. While, percentage changes in PTH had good discriminative power, AUC=0.840 (95% CI: 0.648-1.000), p=0.002 with cut-off point of (-64.8).

CONCLUSION

This study provides additional evidence that postoperative PTH levels can be a good predictor of hypocalcemia in total thyroidectomies. The percentage of decrease in PTH levels from preoperatively to one day postoperatively proved to be the most accurate predictor. Patients with a greater than 64.8% decrease in PTH levels were significantly more likely to develop hypocalcemia. Likewise, patients with a less than 64.8% decrease in PTH levels were safer for discharge.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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